

AMENDMENTS TO THE SPECIFICATION

On page 1, before the heading "FIELD" (i.e., before line 3) please add the following paragraph:

-- This application is the National Stage of International Application No. PCT/EP2004/006943, filed on June 25, 2004. --

Please replace the paragraph beginning at line 19 on page 4 of the specification with the following amended paragraph:

-- an accordingly specified molecule, wherein said amino acid substitutions are conducted within the sequence (A) below comprising T-cell epitopes wherein;

A) (A) = CILGSDGEKNQCVTGEGTPKPESHNDGDFE (SEQ ID NO: 1); --

Please replace the paragraph beginning at line 1 on page 5 of the specification with the following amended paragraph:

-- a modified hirudin molecule having the biological activity of hirudin and comprising at least the amino acid substitutions in SEQ ID NO: 3: I29A and L30A; --

Please replace the paragraph beginning at line 3 on page 5 of the specification with the following amended paragraph:

-- a modified hirudin molecule having the biological activity of hirudin and comprising at least the amino acid substitutions in SEQ ID NO: 3: I29R and L30H; --

Please replace the paragraph beginning at line 5 on page 5 of the specification with the following amended paragraph:

-- a modified hirudin molecule of structure (M; SEQ ID NO: 2):

V V Y T D C T E S G Q N X¹ C X² C E G S V X³ C G Q G N K C X⁴ X⁵ G S D G E K N Q C
X⁶ T G E G T P X⁷ X⁸ E S H N X⁹ G D X¹⁰ E E I P E E Y L Q

wherein;

X¹ = T or L

$X^2 = \text{T or A or H or Q or T or L};$

$X^3 = \text{A or G or H or K or N or P or Q or R or V};$

$X^4 = \text{A or D or E or G or H or K or N or Q or R or S or T or I};$

$X^5 = \text{A or D or E or G or H or K or N or P or Q or R or S or T or L};$

$X^6 = \text{A or T or V};$

$X^7 = \text{T or K};$

$X^8 = \text{A or T or P};$

$X^9 = \text{E or N or R or D};$

$X^{10} = \text{H or F}$

and whereby $X^1 = \text{L}$, $X^2 = \text{L}$, $X^3 = \text{V}$, $X^4 = \text{I}$, $X^5 = \text{L}$, $X^6 = \text{V}$, $X^7 = \text{K}$, $X^8 = \text{P}$, $X^9 = \text{D}$ and $X^{10} = \text{F}$ are simultaneously excluded. --

Please replace the paragraph beginning at line 3 on page 6 of the specification with the following amended paragraph:

-- In nature, the mature hirudin protein is polypeptide of 65 to 66 amino acids. The amino acid sequence of a wild type (WT) hirudin (depicted as single-letter code) is as follows (M82) :
V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I L G S D G E K N Q C V T G E G
T P K P E S H N D G D F E E I P E E Y L Q (SEQ ID NO: 3) --

Please replace the paragraph beginning at line 24 on page 11 of the specification with the following amended paragraph:

-- One significant epitope region (termed R1) was identified in these studies. R1 encompasses residues 28 – 57 of SEQ ID NO: 3 and comprises the sequence
C I L G S D G E K N Q C V T G E G T P K P E S H N D G D F E (SEQ ID NO: 1). --

Please replace the paragraph beginning at line 29 on page 12 of the specification with the following amended paragraph:

-- Taken together, the inventors have been able to define modified hirudin proteins which can be depicted by the following structure (M; SEQ ID NO: 2):

V V Y T D C T E S G Q N X¹ C X² C E G S V X³ C G Q G N K C X⁴ X⁵ G S D G E K N Q C X⁶ T
G E G T P X⁷ X⁸ E S H N X⁹ G D X¹⁰ E E I P E E Y L Q

wherein;

X¹ = T or L

X² = T or A or H or Q or T or L;

X³ = A or G or H or K or N or P or Q or R or V;

X⁴ = A or D or E or G or H or K or N or Q or R or S or T or I;

X⁵ = A or D or E or G or H or K or N or P or Q or R or S or T or L;

X⁶ = A or T or V;

X⁷ = T or K;

X⁸ = A or T or P;

X⁹ = E or N or R or D;

X¹⁰ = H or F

and whereby X¹ = L, X² = L, X³ = V, X⁴ = I, X⁵ = L, X⁶ = V, X⁷ = K, X⁸ = P, X⁹ = D and
X¹⁰ = F are simultaneously excluded. --

Please replace the paragraph beginning at line 20 on page 13 of the specification with the
following amended paragraph:

-- To aid the understanding of the invention, Table 1 below sets out a description of the hirudin
munteins. The derivation and properties of these proteins are also more fully disclosed in the
examples. In Table 1, the heading labeled "Substitution(s)" refers to substitutions in
SEQ ID NO: 3. --

Please replace the contents of Table A, beginning at the line labeled "5" on page 14 and
continuing through line 18 on page 20 of the specification with the following amended table:

M 1 (SEQ ID NO: 4)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C A A G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 2 (SEQ ID NO: 5)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C R H G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 3 (SEQ ID NO: 6)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C E K G S D G
E K N Q C A T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 4 (SEQ ID NO: 7)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C E K G S D G
E K N Q C T T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 5 (SEQ ID NO: 8)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C E K G S D G
E K N Q C V T G E G T P K P E S H N E G D F E E I P E E Y L Q

M 6 (SEQ ID NO: 9)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C E K G S D G
E K N Q C V T G E G T P K P E S H N N G D F E E I P E E Y L Q

M 7 (SEQ ID NO: 10)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C R K G S D G
E K N Q C A T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 8 (SEQ ID NO: 11)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C R K G S D G
E K N Q C T T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 9 (SEQ ID NO: 12)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C R K G S D G
E K N Q C V T G E G T P K P E S H N E G D F E E I P E E Y L Q

M 10 (SEQ ID NO: 13)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C R K G S D G
E K N Q C V T G E G T P K P E S H N N G D F E E I P E E Y L Q

M 11 (SEQ ID NO: 14)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C R R G S D G
E K N Q C T T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 12 (SEQ ID NO: 15)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C A K G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 13 (SEQ ID NO: 16)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C A Q G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 14 (SEQ ID NO: 17)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C A R G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 15 (SEQ ID NO: 18)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C A T G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 16 (SEQ ID NO: 19)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C D A G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 17 (SEQ ID NO: 20)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C D Q G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 18 (SEQ ID NO: 21)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C D R G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 19 (SEQ ID NO: 22)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C E K G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 20 (SEQ ID NO: 23)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C E Q G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 21 (SEQ ID NO: 24)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C E R G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 22 (SEQ ID NO: 25)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C E T G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 23 (SEQ ID NO: 26)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C R K G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 24 (SEQ ID NO: 27)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C R Q G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 25 (SEQ ID NO: 28)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C R R G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 26 (SEQ ID NO: 29)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C R T G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 27 (SEQ ID NO: 30)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C S A G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 28 (SEQ ID NO: 31)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C S K G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 29 (SEQ ID NO: 32)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C S Q G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 30 (SEQ ID NO: 33)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C S R G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 31 (SEQ ID NO: 34)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C S T G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 32 (SEQ ID NO: 35)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C T A G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 33 (SEQ ID NO: 36)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C T K G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 34 (SEQ ID NO: 37)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C T Q G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 35 (SEQ ID NO: 38)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C T R G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 36 (SEQ ID NO: 39)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C T T G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 37 (SEQ ID NO: 40)

V V Y T D C T E S G Q N T C L C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 38 (SEQ ID NO: 41)

V V Y T D C T E S G Q N L C A C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 39 (SEQ ID NO: 42)

V V Y T D C T E S G Q N L C H C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 40 (SEQ ID NO: 43)

V V Y T D C T E S G Q N L C Q C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 41 (SEQ ID NO: 44)

V V Y T D C T E S G Q N L C T C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 42 (SEQ ID NO: 45)

V V Y T D C T E S G Q N L C L C E G S V A C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 43 (SEQ ID NO: 46)

V V Y T D C T E S G Q N L C L C E G S V G C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 44 (SEQ ID NO: 47)

V V Y T D C T E S G Q N L C L C E G S V H C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 45 (SEQ ID NO: 48)

V V Y T D C T E S G Q N L C L C E G S V K C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 46 (SEQ ID NO: 49)

V V Y T D C T E S G Q N L C L C E G S V N C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 47 (SEQ ID NO: 50)

V V Y T D C T E S G Q N L C L C E G S V P C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 48 (SEQ ID NO: 51)

V V Y T D C T E S G Q N L C L C E G S V Q C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 49 (SEQ ID NO: 52)

V V Y T D C T E S G Q N L C L C E G S V R C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 50 (SEQ ID NO: 53)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C A L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 51 (SEQ ID NO: 54)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C D L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 52 (SEQ ID NO: 55)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C E L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 53 (SEQ ID NO: 56)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C G L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 54 (SEQ ID NO: 57)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C H L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 55 (SEQ ID NO: 58)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C K L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 56 (SEQ ID NO: 59)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C N L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 57 (SEQ ID NO: 60)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C Q L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 58 (SEQ ID NO: 61)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C R L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 59 (SEQ ID NO: 62)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C S L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 60 (SEQ ID NO: 63)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C T L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 61 (SEQ ID NO: 64)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I A G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 62 (SEQ ID NO: 65)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I D G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 63 (SEQ ID NO: 66)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I E G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 64 (SEQ ID NO: 67)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I G G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 65 (SEQ ID NO: 68)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I H G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 66 (SEQ ID NO: 69)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I K G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 67 (SEQ ID NO: 70)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I N G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 68 (SEQ ID NO: 71)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I P G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 69 (SEQ ID NO: 72)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I Q G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 70 (SEQ ID NO: 73)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I R G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 71 (SEQ ID NO: 74)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I S G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 72 (SEQ ID NO: 75)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I T G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 73 (SEQ ID NO: 76)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I L G S D G
E K N Q C A T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 74 (SEQ ID NO: 77)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I L G S D G
E K N Q C T T G E G T P K P E S H N D G D F E E I P E E Y L Q

M 75 (SEQ ID NO: 78)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P T P E S H N D G D F E E I P E E Y L Q

M 76 (SEQ ID NO: 79)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K A E S H N D G D F E E I P E E Y L Q

M 77 (SEQ ID NO: 80)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K T E S H N D G D F E E I P E E Y L Q

M 78 (SEQ ID NO: 81)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N E G D F E E I P E E Y L Q

M 79 (SEQ ID NO: 82)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N N G D F E E I P E E Y L Q

M 80 (SEQ ID NO: 83)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N R G D F E E I P E E Y L Q

M 81 (SEQ ID NO: 84)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D H E E I P E E Y L Q

M 82 (SEQ ID NO: 3)

V V Y T D C T E S G Q N L C L C E G S V V C G Q G N K C I L G S D G
E K N Q C V T G E G T P K P E S H N D G D F E E I P E E Y L Q

(A) (SEQ ID NO: 1):

C I L G S D G E K N Q C V T G E G T P K P E S H N D G D F E

Please replace the paragraph beginning at line 24 on page 20 of the specification with the following amended paragraph:

-- The mature sequence of [Val¹ Val²]-hirudin (SEQ ID NO: 3) with regions of immunogenicity highlighted in bold. The most preferred modifications are to residues 29 and 30 (underlined). The preferred alternative substitutions are indicated above the sequence. --

Please replace the paragraph beginning at line 23 on page 21 of the specification with the following amended paragraph:

-- For protein expression, the native 20 amino acid secretion signal, (MFSLKLFVVFLAVCICVSQA, SEQ ID NO: 85, of a hirudin variant from the Asian buffalo leech (*Hirudinaria manillensis*) was added by PCR and this construct was then sub-cloned into the expression vector pREP4 (Invitrogen, Paisley, UK). Later a modified secretion signal (MVSLKLFVVFLAVCICVSQA; SEQ ID NO: 86) was used in order to create a more efficient Kozak consensus sequence for protein expression in mammalian cell lines [~~Kozak M. (1987) *Nucleic Acids Research*; 15: 8125-8148; Kozak M. (1991) *Journal of Cell Biology*; 115: 887-903; Kozak M. (1990) *Proc. Natl. Acad. Sci. (USA)*; 87: 8301-8305~~ Kozak, M. (1987) *Nucleic Acids Research*; 15: 8125-8148; Kozak M. (1991) *Journal of Cell Biology*; 115: 887-903; Kozak, M. (1990) *Proc. Natl. Acad. Sci. (USA)*; 87: 8301-8305], where the mutation of F² (TTC) to a V (GTC) placed a guanosine residue at position +4 in the consensus sequence. --

Please replace the paragraph beginning at line 12 on page 24 of the specification with the following amended paragraph:

-- Of these active proteins, 45 were muteins comprising a single amino acid substitution; 27 comprised two amino acid substitutions and 9 comprised three amino acid substitutions. The sequence of each of these active hirudin muteins is provided in M 1 - 81. The relative activities of each functioning mutein are provided in Table 2 in which the heading labeled "Substitution" refers to substitutions in SEQ ID NO: 3. --

Please replace Table 3, at the top of page 26 with the following amended table:

Peptide No	<u>SEQ ID NO:</u>	Peptide sequence	Peptide No	<u>SEQ ID NO:</u>	Peptide sequence
1	<u>87</u>	VVYTDCTESGQNLCL	11	<u>97</u>	CILGSDGEKNQCVTG
2	<u>88</u>	LYYTDCTESGQNLCL	12	<u>98</u>	GSDGEKNQCVTGEGT
3	<u>89</u>	TDCTESGQNLCLCEG	13	<u>99</u>	GEKNQCVTGEGTPKP
4	<u>90</u>	TESGQNLCLCEGSNV	14	<u>100</u>	NQCVTGEGTPKPESH
5	<u>91</u>	GQNLCLCEGSNVCGQ	15	<u>101</u>	VTGEGTPKPESHNDG
6	<u>92</u>	LCLCEGSNVCGQGNK	16	<u>102</u>	EGTPKPESHNDGDFE
7	<u>93</u>	CEGSNVCGQGNKCIL	17	<u>103</u>	PKPESHNDGDFEEIP
8	<u>94</u>	SNVCGQGNKCILGSD	18	<u>104</u>	ESHNDGDFEEIPEEY
9	<u>95</u>	CGQGNKCILGSDGEK	19	<u>105</u>	NDGDFEEIPEEYYLQ
10	<u>96</u>	GNKCILGSDGEKNQC			

Please replace Table 4 beginning after line 27 on page 27 with the following amended table:

Wild Type Sequence	% donor response in time course	Modified Sequences	% donor response in time course
CILGSDGEKNQCVTG <u>SEQ ID NO: 97</u>	25	CAAGSDGEKNQCVTG <u>SEQ ID NO: 106</u>	5
		CEKGS DGEKNQCVTG <u>SEQ ID NO: 107</u>	10
		CRHGS DGEKNQCVTG <u>SEQ ID NO: 108</u>	5